# Why Cancer?

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**INTRODUCTION:** One requires very few words to justify writing such an article as this: no one can afford not to be at least curious as to the "Why" and "How" of the most dreaded, almost invariably fatal ailment of the twentieth century. While the "How" is of the utmost interest to the clinician there is much to be said in favour of educating the layman as to the possible "Why" of cancer and hence its prevention. To people in the medical field this can prove a most provoking and thought-stimulating question.

It has long been held that "a substance or an activity" is the cause of cancer. Lately the trend has been that of talking about "carcinogenic compounds". Both these views are extreme attitudes and it is more likely that "cancer" comprises a large group of apparently diverse pathological conditions, all, however, being just different manifestations of a simple basic process. Histopathologically, hyperchromatism, aneuploidy, increased nucleus to cytoplasm ratio, increased nuclear mass and increased number of mitoses, characterizes cancerous cells. Physiologically, cancer cells possess in common a loss of contact inhibition, a lack of normal cohesiveness, increased amoeboid motility, lowered calcium content, increased membrane permeability and an increase in cytolytic effects; they all possess the capacity to invade and destroy surrounding normal tissue. In general, tissues are more susceptible to neoplastic conversion, the younger and the more actively dividing they are. A further similarity among cancers appears in the precancerous stages, well-described by many in cervix, breast, mouth, lung, skin, bladder and vulva, and resembling each other very much. Once more cancers are all focal and localized at inception (though clinically this cannot always be confirmed due to the advanced stage of the lesion when seen). This seems to indicate that the initial steps in the carcinogenic sequence always takes place in a local area, one cell or a single group of cells. Finally, **Greenstein** has shown that the enzyme patterns of malignant tumours from different tissues with different normal patterns tend to converge towards a common cancer system. In fact, cancer appears to be a tissue response to a very complex mixture of circumstances that coincide and interrelate in a specific manner; it is common to all living tissue and any cell capable of division is subject to it. The immediate implication of these statements is that not only can we not implicate just one cause, but that in addition no carcinogenic threshold dose or dose-result relationship can be stated as this varies with other types and amounts of carcinogens acting at the same site.

The production of cancer basically requires three conditions:

(a) the presence and adequate dosage of an external agent or **initiator,**

(b) an internal predisposition or **promoting factor,**

(c) the passage of relatively long periods of time i.e. **a phase of initiation.**

In fact **Berenblum** states that some initiators though responsible for the start of the cancer process, require, at low dosage, a promoting factor to complete it. Most initiators do not need promoters but all promoters need initiators. The value of this statement appears later with a consideration of the possible agents in each classification.

With these basic ideas in hand we can build a simple formula to guide our thoughts; this, however, will essentially be an extreme over-simplification and take the following form:


One prefers the use of the term "neoplastic conversion" rather than "neoplasm" (new growth or cancer) as this bears out the exact microscopical nature of cancer i.e. that of an an irreversible change in tumour cells. By neoplasm or new growth we often have in mind, unfortunately, a more advanced stage — that of cellular proliferation with tumour expansion, infiltration and spread. I say "unfortunately" because the prognosis then is always much nearer to zero and this is where the question "Why cancer?" is so important: the possibility of effective prevention of cancer will only be in sight when the answer to this question is truly found.

The final common pathway of most cancer theories consists of a genetic change in the developing cancer cell, a somatic mutation. Whether somatic mutation is cause or consequence, it is generally a prominent feature of the neoplastic conversion. On the other hand germ-cell mutation, which is hereditary from generation to generation, plays an important role in the development of certain rare human cancers such as retinoblastoma of infants and familial multiple polyposis of the colon, where so strongly does the genetic ability favour cancer in these families that other external and internal factors never alter the emersion of the tumour trait to any significant degree. Thus, it seems now generally accepted by workers in this field that malignancy is a change in the normal process governing "information and data" within every cell. This is usually part of the genetic constitution of each cell unit and interference with it can clearly lead to such abnormal behaviour as direct stimulation of proliferation, or proliferation as a result of release from controls inside or outside the cell. It has also become conspicuous that viruses (by replacing or redirecting activity of genetic material), chemical carcinogens (by combining with DNA) and ionizing radiations (by causing chromosomal breaks) are all capable of causing

changes in the genetic material, the DNA or information centre of the cell.

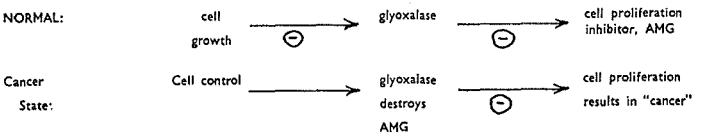
A cursory look at a list of theories (which makes no attempt at being exhaustive but rather is a cross-section of old and modern theories) indicates well the complexity of multiple factor interaction that is possible and the ingenuity needed for integration of all major factors into a coherent single theory; none of these theories can be grouped into the biochemical ones, those based on immunology and a miscellaneous third set.

**BIOCHEMICAL THEORIES:** Somatic mutation has been explained simply on the basis of an interaction between an external chemical compound and the DNA of the cell. It has also been theorised that latent viruses may be activated as a result of deletion of repressor or controlling factors by the foreign chemical substance. Others have suggested that it is an alteration in the structure of *chalones* (specific chemical messengers controlling cell division) which leads to the cancerous state. Abell and Heidelberger have postulated a deletion of enzymatic growth control factors by such chemical binding between carcinogenic hydrocarbons and these enzymes, the deleted factors possibly being an RNA molecule. **Szent-Györgyi** *et al* claim that a cell proliferation inhibitor, probably an aldoketone methyl glyoxal (AMG), exists; its action can be stopped by a glyoxalase, so that if the cell loses the ability to control the glyoxalase, uncontrolled cell growth could result (see fig. 1).

The cell contact inhibition theory is similar in that here cancer cells lose this mutual restraint and abnormal tissue accumulation occurs once more due to loss of the normal inhibition. On a different note some workers have postulated an abnormal response to altered hormonal activity. However, this theory appears to be limited to the hormone dependant ones like, for example, cancer of the breast. To summarise these six or seven theories in one sentence: a change in the biochemical activities of the cancerous cell is held responsible for the ensuing proliferation. This has been experimentally confirmed but one must now find out whether the change is the cause or the result of the abnormality.

**IMMUNOLOGICAL THEORIES:** **Cohnheim** suggested that "rests" derived from tissues misplaced during embryonic development proliferated to tumour later. This may explain teratomas but not their malignancy, nor why not all become malignant. **Tyler** has drawn an analogy between transplant rejection and cancer. He postulated that parallel to the application of the clonal selection theory of acquired immunity to lymphocytes, tumour specific antigens (formed possibly by a combination of chemical compounds and cell protein) form in regional lymph nodes which enlarge and "tumour graft" rejection occurs. The graft takes in the event that continued primary tumour growth throws off excessive tumour antigen which overwhelms the sensitized clones of antigens. This theory deals almost exclusively with metastasis. Metastasis of normal and benign tumours probably does not occur

**Fig. I.**




(except for the phenomenon of endometriosis) because of cell contact inhibition, a property characteristic of normal but not of cancerous cells. Thus the possibility exists that clinical cancer only develops when the tumour can overwhelm the immune defences of the host, which by the present evidence seems to be generally weak. The long latent period in most (clinically detectable) cancers may result from antibody production during the preclinical stages.

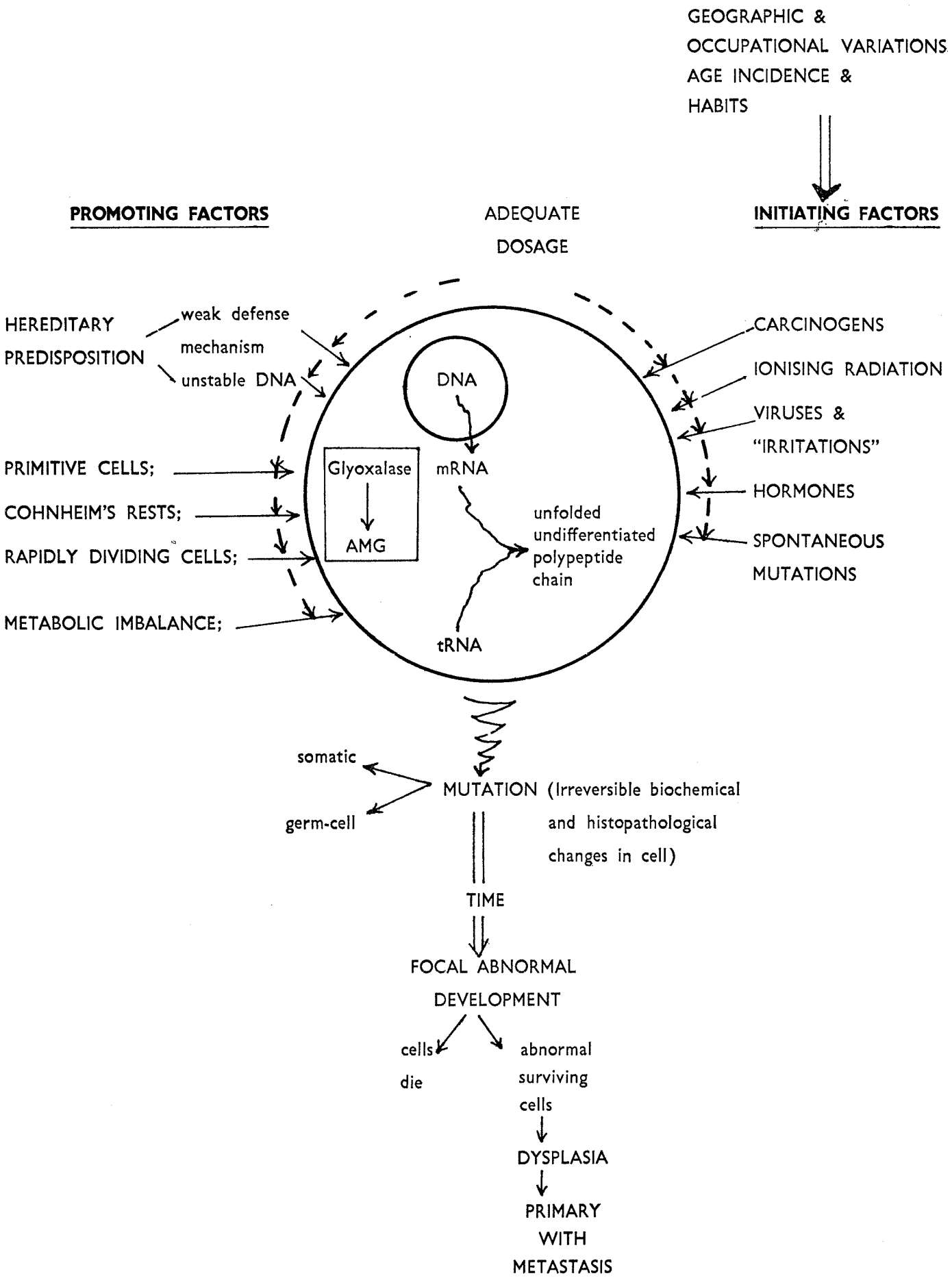
**OTHERS:** Chronic irritation, though often held responsible for cancerous change, is not always implicated; when it is, the primary factor may still be the irritant chemical substance itself rather than the mechanical irritation. Cellular infection by carcinogenic viruses (a form of chronic irritation, if you like) leading to abnormal multiplication, is the basis of the infective theory. The experimental observation that tissue culture cells which under-went virus-induced 'malignant" transformation can lose all signs of the abortive infection without changing their malignant potential, points to the possibility that viruses might induce neoplasms in humans by a "hit and run" effect: chronic viral infection (e.g. with **herpes** virus) might lead to the development of cancerous cell growth indistinguishable from neoplasms occurring through the agency of chemical carcinogens.

No epidemiological or statistical evidence has as yet confirmed the view that there can be an inborn genetically transmitted tendency for an individual's cells to become cancerous. This evidence must be hard to come by though, since this tendency may alone be just the promoting factor, and so (according to **Berenblum**) not capable of bringing about cancerous change.

**Thiersch** suggested that a balance between epithelial and connective tissue elements existing normally is lost when cancerous change occurs. Still he makes no attempt to state whether this is the cause or consequence of cancer. **Mendelsohn** in the field of cell population dynamics suggests that in any tissue a fraction of cells are actively proliferating while the other portion consists of cells in the resting stage; the result is that the rate of growth depends on the fraction of proliferating ones of the whole population. The latter fraction is usually small, varies from tissue to tissue, and increases substantially with injury and repair. In neoplasms a higher fraction results with overgrowth of the normal tissue bed by the dividing tumour cells.

Promising unorthodox information has very recently been obtained by **Clarence D. Cone, Jnr.,** head of the molecular biophysics laboratory at Langley Research Centre, in Vinginia. Mr. Cone has found that normal cells divide at a slow healthy rate when electrical charge on

Fig. II.


GEOGRAPHIC &
OCCUPATIONAL VARIATIONS
AGE INCIDENCE &
HABITS
PROMOTING FACTORS
ADEQUATE
DOSAGE
INITIATING FACTORS
HEREDITARY
PREDISPOSITION
weak defense
mechanism
unstable DNA
PRIMITIVE CELLS;
COHNHEIM'S RESTS;
RAPIDLY DIVIDING CELLS;
METABOLIC IMBALANCE;
DNA
Glyoxalase
AMG
mRNA
tRNA
unfolded
undifferentiated
polypeptide
chain
CARCINOGENS
IONISING RADIATION
VIRUSES &
"IRRITATIONS"
HORMONES
SPONTANEOUS
MUTATIONS
somatic
germ-cell
MUTATION (Irreversible biochemical
and histopathological
changes in cell)
TIME
FOCAL ABNORMAL
DEVELOPMENT
cells
die
abnormal
surviving
cells
DYSPLASIA
PRIMARY
WITH
METASTASIS

their surface (produced by the continual removal of salts across the membranes) is high; they divide at a much faster (cancerous) rate when this is low. In addition, the living cells tend to adhere strongly to one another when the surface voltage is high and vice versa. Mr Cone therefore proposed that electrical activity is the central mechanism for control of cell division.

It seems also possible that chemical and other carcinogens, instead of inducing abnormal cancerous changes, act by allowing the survival and proliferation of spontaneous mutants while suppressing proliferation of normal cells, or may in general interfere in the interests of some of these mutants. From a teleological point of view it has been suggested that cancerous change is just a form of local defence, mechanical and immunological, after a more general defence mechanism has failed against the particular carcinogen. This view must be correlated with the observation that a neoplasm always grows away from the site of application of the carcinogen.

So much for theories; we are now in a good position to try and integrate all the various possible factors which may act at various sites in the cell to produce the clinical cancer (see fig II). In the normal way of events the messenger RNA takes a mirror image of the DNA in the nucleus to the transfer RNA which carries the amino acids. The transfer RNA in the cytoplasm forms a mirror image of the messenger RNA and the amino acids are then "zipped up" into polypeptides which are then folded into proteins. Hence, carcinogenic action may be directed against the DNA, the RNA or the as yet unfolded, undifferentiated ploypeptide chain. Of special mention is the possibility of "loss of cell control over the glyoxalase", postulated by **Szent-Györgyi.**

The promoting factors include a hereditary predisposition due to a weak circulating defence mechanism or an unstable DNA; rapidly dividing or primitive cells (including Cohnheim's Rests); and a general metabolic imbalance in the form of hormones, temperature regulation, pH, gaseous transport and exchange and electrolyte transport.

The initiating factors may take the form of chemical or physical carcinogens, ionising radiation, viruses and inflammatory chronic conditions or hormones; these factors admit of geographic and occupational variations, age incidences and variation with social habits. Finally gene mutations may occur spontaneously. This may be an initiator or a promoter initiated by a combination with a promoter; there must be in each case an adequate dosage of each factor. When all these requirements are met, the stage is set for a mutation to occur (be it somatic or germ-cell). After a variable latent period (required for the abnormal cells to overcome local general defence mechanism, or according to the teleological view: the time required for this form of defence mechanism to "build up") a focal abnormality appears starting as a dysplasia and passing on to a "primary with metastasis".

**CONCLUSION:** A study of the various interrelated ways leading to the inception of cancer should point out the high risk persons and so facilitate early diagnosis, explain the increasing incidence of some types of cancer and shed considerable light on its eventual prevention.

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